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Date of Signature and Deposit: 11/18/04

Jean C. Baker
Attorney of Record

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Teresa Compton, et al.
Serial No.:	09/942,146
Filed:	August 29, 2001
For:	HUMAN CYTOMEGALOVIRUS GLYCOPROTEIN O AS A NEW DRUG TARGET AND SUBUNIT VACCINE
Group Art Unit:	1648
Examiner:	B. Li

DECLARATION OF DR. TERESA COMPTON

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Teresa Compton, declare that:

1. I am a named inventor in the above-identified case. I am a Professor in the Department of Oncology and Chair of the Cellular Molecular Biology graduate program at McArdle Laboratory for Cancer Research at the University of Wisconsin. I have been a faculty member at University of Wisconsin for 14 years and have focused my research in molecular virology (most particularly cytomegalovirus biology) for the past 17 years.

2. Attorney Jean C. Baker has asked me to review the current Office Action in the above-identified case and comment on the Examiner's cited references. I disagree with the Examiner's characterization of the references as either teaching or making obvious the present invention.

3. Summary of Glycoprotein Complexes Displayed in Human Cytomegalovirus

As an aid to the Examiner I will provide a brief summary of glycoprotein complexes displayed in Human cytomegalovirus (HCMV). HCMV is a structurally complex virus displaying at least twelve glycoproteins in its envelope. This structural complexity and immunologic diversity is in striking contrast to most viruses such as human immunodeficiency virus (HIV) and influenza virus that display one or two envelope proteins. Earlier work showed that the envelope glycoproteins were frequently organized into homo- and hetero- oligomeric complexes that were typically disulfide bonded into higher order structures (Britt, W. J., Virology 135:369-378, 1984; Britt, W. J., and D. Auger., J. Virol. 58:185-91, 1986; Gretch, D. R., et al., J. Gen. Virol. 69:1205-1215, 1988; Gretch, D. R., et al., J. Virol. 62:1956-62, 1988; Gretch, D. R., et al., J. Virol. 62:875-81, 1988 [cited by the Examiner]).

4. The complexes were also distinguished on the basis of reactivity with monoclonal antibodies (i.e., Gonczol, E., et al., Vaccine 8:130-6, 1990 [cited by the Examiner]; Gretch, D. R., et al., supra, 1988 [cited by the Examiner]; Rasmussen, L., et al., Virology 163:308-18, 1988). For example, Gonczol taught that a complex formally called gA elicited neutralizing antibodies. This complex was later determined to be encoded by the UL55 gene and is structurally related to the gB proteins of all herpesviruses. The complex discussed by Gonczol, et al. is completely unrelated to the gO-containing complex. The genetic identity of other complexes remained undefined until recent years. Similarly, Gretch, et al., teaches that the glycoprotein complexes of HCMV can be distinguished on the basis of antibody reactivity. As with Gonczol, et al., the genetic identities were not determined nor predicted.

5. Why was the delineation of the genes encoding HCMV glycoproteins a difficult task? Would it not be obvious what gene encoded a particular glycoprotein based on its molecular mass? The answer to the latter question is no, it is not obvious. The reasons are twofold.

6. The first reason relates to ambiguities involving the weight of glycoproteins. The molecular mass of glycoproteins was estimated from the electrophoretic migration in SDS-PAGE. The apparent electrophoretic mobility is affected by the size of the polypeptide backbone and the oligosaccharide modifications. The extent to which carbohydrate contributes to the mass is a direct reflection of the number of N-linked oligosaccharide chains as well as any additional post-translational modifications such as O-linked oligosaccharides or phosphorylation. On a percentage basis, carbohydrate can contribute as little as 5 – 10 %, or as great as 60 – 80%, of the mass. Thus, unless one can determine how much of the overall mass is derived from carbohydrate and how much is derived from the polypeptide itself, which would be reflected in the gene size, it is not obvious what gene may encode that protein.

7. The second reason this is not straightforward is learned directly from the coding capacity of the HCMV genome. The genome of HCMV is approximately 225,000 nucleotides (Cha, T.-A., et al., J. Virol. 70:78-83, 1996; Chee, M. S., et al., Current Topics in Microbiology and Immunology 154:125-169, 1990; Murphy, E., et al., Proc. Natl. Acad. Sci. USA 100:13585-90, 2003; Murphy, E., et al., Proc. Natl. Acad. Sci. USA 100:14976-81, 2003). A recent reevaluation of the coding capacity of the strain of virus used in our research (AD169) showed that there are 192 unique open reading frames of which as many as 50 have predictive features of membrane glycoproteins (presence of potential signal sequence, N-linked carbohydrate addition

sites and transmembrane anchor domains). Thus, even if one has some idea of the gene size, it is not obvious what of the many candidate genes it would be.

8. History of the gCIII Complex

The gCIII complex is one of the immunologically distinct complexes in HCMV. Gretch et al. taught that the complex contained three differentially migrating polypeptides of 125-145 kDa, 86 kDa and 34 kDa. Ultimately, Spaete, et al. taught that the 86 kDa protein was encoded by the UL75 gene (gH) and the 34 kDa protein was encoded by the Ul115 gene (gL) (Spaete, R. R., et al., Virology 193:853-861, 1993). The identity of the 125-145 kDa gene remained undefined and it was widely speculated that the protein may be an oligomer of gH and gL since the sum of their mass was approximately 125 kDa. Li, et al. and Huber, et al. taught that the 125-145 kDa protein was neither gH nor gL nor a modified form of the two proteins and therefore was likely to be encoded by a distinct gene product (Huber, M. T., and T. Compton, J. Virol. 71:5391-8, 1997; Li, L., et al., J. Virol. 71:3090-7, 1997 [both cited by the Examiner]). There were at least 35 genes that could potentially encode this protein and, thus, is was not obvious from this work or from any earlier work what gene encoded the protein that Huber ultimately named gO and mapped to the UL74 gene by detailed biochemical analysis including protein sequencing (Huber, M. T., and T. Compton, J. Virol. 72:8191-7, 1998).

9. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false

statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Respectfully submitted,

Date: Nov. 17, 2004

Teresa Compton

Teresa Compton